ATTORNEY DOCKET NO. 21127.0007U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Lee, et al.	)	Art Unit: 1615
	)	
Application No. 10/332,547	)	Examiner: Channavajjala, LS
	)	
Filing Date: September 30, 2003	)	Confirmation No. 5510
	)	
For: DERMAL APPLICATION SYSTEM FOR AMINOLEVULINIC ACID	)	

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer Number 23859

Sir:

I, MECHTILD LOEBEL, hereby declare that:

1. I am an employee of photonamic GmbH & Co KG (further called "photonamic"), and hold a Ph.D. in Pharmacy from the University in Kiel, Germany. I have over 20 years experience in the field of pharmaceutical development, with an emphasis on patch development in the last 5 years. At photonamic, I am responsible for all aspects of pharmaceutical development and report directly to the CEO.

2. Photonamic is the assignee of the above-referenced application relating to dermal application system comprising crystalline aminolaevulinic acid (ALA). I coordinated the

experiments discussed herein, which were performed by one of the world's leading producer of dermal therapeutic systems on photonamic's behalf.

3. I have reviewed the Final Office Action mailed July 31, 2007 and the Advisory Action mailed December 21, 2007 in connection with the above-referenced application and the following references cited in that Office Action:

a) WO 95/05813 (WO), by Juan Mantelle and Allyn Golub, and

b) US 5,856,566 ('566), by Allyn Golub.

4. I understand that claims 1-6, 9 and 11-12 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over WO in view of '566. Specifically, I understand that the rejection is based in part on the contention that 1) WO teaches a pharmaceutical dermal application system comprising ALA and indicates a desire for the ALA preparation to be stable due to the normally rapid degradation of ALA, and 2) '566 suggests employing micronized crystals of ALA in order to overcome the degradation problem.

5. I present in this declaration evidence indicating that dermal application systems comprising ALA crystals in the size range of tens to hundreds of microns have a significantly and surprisingly higher rate of ALA release compared to a dermal application system with dissolved ALA, such as the system described in WO 95/05813 (WO). Figure 1 of **Exhibit A** (attached hereto) shows the release/ permeation profile of 5-ALA from a silicon polymer patch, wherein, in one case, a 5-ALA solution was incorporated, and in the other case, 5-ALA crystals with a size of 90-160 μm were suspended in the matrix. The determination of crystal size was carried out by sieving (see page 10, line 1 of the above-referenced application). The crystals

were ground and classified (see page 6, 3rd paragraph of Example 1), i.e., the size of crystals used was determined by sieving with a defined mesh size. Accordingly, particles sized 90-160 μm passed through a mesh size of 160 μm and did not pass through a mesh size of 90 μm. In this range, their distribution was approximately random.

As shown in Figure 1 of **Exhibit A**, a silicon polymer patch comprising ALA crystals in the size of 90-160 μm had a dramatically higher release rate compared to the dermal application system prepared with dissolved ALA ("dissolved ALA-patch"). After 1 hour, 9 $\mu g/cm^2$ was released and had permeated through an artificial membrane when the dissolved ALA-patch was used, while 515 $\mu g/cm^2$ was released/ permeated from the patch comprising ALA crystals. Of note, the release/ permeation rate measured for the dissolved ALA-patch (9 $\mu g/cm^2$) was even higher than that disclosed by the WO reference, which states that the release rate should be at least 0.1 $\mu g/cm^2$ per hour.

As can be seen from Figure 2B of **Exhibit A**, ALA crystals from approximately 20 to 200 μm in size were used for preparation of a polyacrylate patch. As shown in Figure 2A of **Exhibit A**, the release rate was about 1500 $\mu g/cm^2$ of ALA in the first hour, with 72.5 % of all ALA released in the first 30 min.

6. I further declare that the demonstrated effect of significantly increasing the release rate by dispersing ALA crystals of a size of 30-200 μm in a dermal application system was not foreseeable on the basis of WO and '566.

7. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the

statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 29.02.2008

M. Loebel

MECHTILD LOEBEL

EXHIBIT A

Figure 1:

Release / permeation profile of ALA from a silicon polymer patch (BioPSA®) through an artificial membrane. The patches were manufactured by two different methods: for the first method ("dissolved", containing 15% ALA) an ALA-solution was incorporated in the matrix and then the patches were prepared. For the second method ("suspended", containing 20% ALA) a matrix with suspended ALA particles sized 90-160 µm was used.

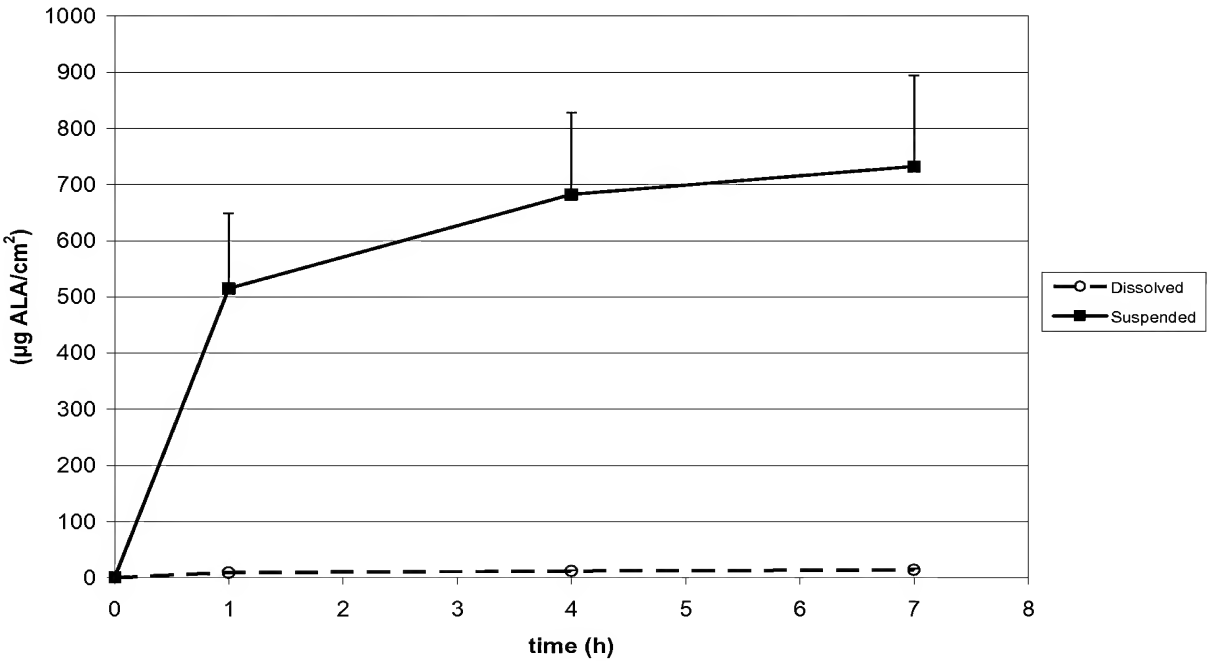

Figure 2A shows release profile of ALA from a polyacrylate patch (DuroTak®). Patches were prepared using ALA particles, passed through a 200 μm sieve, suspended in the matrix. Within 30 minutes 72,5 % of all ALA was released.

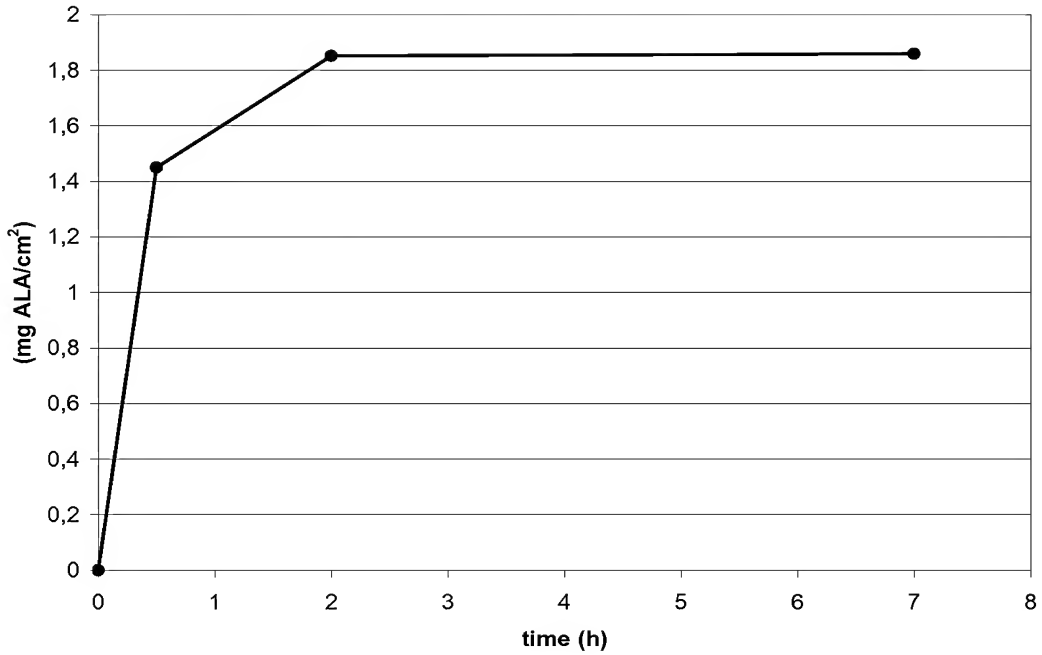

Figure 2B shows particle size distribution of the batch of ALA used for patches of Figure 2A.